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Role of Tissue Factor in Atherothrombosis

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Abstract

Atherothrombosis describes the acute thrombotic event that occurs after rupture of an atherosclerotic plaque. It often leads to arterial occlusion and subsequent clinical manifestations of myocardial infarction, stroke, and sudden death. Tissue factor (TF) is the receptor for plasma factor VIIa (FVIIa) and, once formed, the TF:FVIIa complex activates the coagulation cascade. TF is present at high levels within atherosclerotic lesions and is also present on circulating monocytes and microparticles in patients with advanced cardiovascular disease (CVD). Formation of the TF:FVIIa complex plays a central role in atherothrombosis. This review will describe the cellular sources of TF, the potential of TF-positive microparticles as a biomarker of thrombotic risk, and current pharmacologic approaches to inhibit TF as a therapeutic intervention in patients with CVD.

Introduction

Atherothrombosis is the result of atherosclerotic plaque disruption and subsequent arterial thrombosis, which culminates in arterial occlusion and myocardial infarction or stroke. Atherosclerosis and subsequent atherothrombosis is one of the most devastating disease states in the Western world accounting for more than 25% of deaths in the United States in any given year, which is the leading cause of death in both men and women [1-3]. In addition, the projected cost of coronary heart disease in the United States was over $100 billion in 2010 due to health care services, medications, and lost worker production [4]. Characterized as a disease of cholesterol deposits in macrophages and the vessel wall in small and medium sized arteries, it is more comparable to an autoimmune insult on the main transport vesicle for cholesterol, low density lipoprotein (LDL), after progressive oxidation. Atherosclerosis is undetectable without specific radiographic examinations or invasive procedures. Recently, atherosclerosis has been redefined as an inflammatory disease due to the combined cellular and molecular analyses of atherosclerotic lesions (reviewed in detail [5]). Recently, much clinical interest has been generated regarding the crosstalk between coagulation and inflammation in the pathogenesis of vascular diseases [6]. In particular, our

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laboratory is interested in the relationship between atherosclerosis and the procoagulant protein tissue factor (TF).

TF is the primary initiator of the extrinsic pathway of coagulation [7-8]. When it binds its ligand factor VIIa (FVIIa) a complex is formed that activates both FIX and FX resulting in the generation of thrombin and ultimately cross-linked fibrin [9]. TF is not normally exposed to flowing blood, but rather expressed by cells in the media, such as vascular smooth muscle cells (VSMCs), or cells in the adventitia, such as adventitial fibroblasts. It has been proposed to form a protective 'haemostatic envelope' to reduce blood loss in the event of vascular injury [10-11]. Importantly, TF expression is also induced in circulating monocytes, the major source of intravascular TF [12], during cardiovascular disease (CVD) and in the macrophages within atherosclerotic plaques [13]. It is speculated that TF is the main protein involved in triggering thrombosis after plaque rupture.

This review will discuss (1) the cellular sources of TF in atherosclerotic plaques, (2) the potential use of TF-positive microparticles (MPs) as a biomarker for CVD, and (3) currently used therapeutics to decrease the amount of TF in atherosclerotic plaques and in the circulation.

TF Expression within Atherosclerotic Plaques

The initiating event in atherosclerosis is still a mystery to both scientific and clinical researchers. However, after several decades of research, there are three prevailing hypotheses currently being tested: (1) the response-to-injury hypothesis [14-16], (2) the response-to-retention hypothesis [17-18], and (3) the oxidative modification hypothesis [18-19]. These models are elegantly summarized by Stocker and Keaney [20]. Briefly, the response to injury hypothesis suggests the initiation of atherosclerosis begins with endothelial injury or dysfunction resulting in LDL deposition (resulting in progressive oxidative modification) into the subendothelial space leading to a constant 'autoimmune-like' attempt to continually heal this injury (critical event: endothelial injury/dysfunction). In contrast, the response-to-retention hypothesis suggests LDL infiltrates specific sites within arteries due to transcytosis and arterial retention from proteoglycan binding results in lipoprotein aggregation and modification leading to triggering of the proinflammatory cascade (critical event: LDL-matrix interactions). Finally, the oxidative modification hypothesis results from trapped subendothelial LDL becoming oxidized (oxLDL) resulting in monocyte chemotaxis and foam cell formation (critical event: LDL oxidation). Regardless of the hypothesis, the end result is leukocyte adhesion, transmigration, foam cell formation, inflammation, VSMC migration, formation of a fatty streak, apoptosis, necrosis, release of proteases, and eventual weakening of the fibrous cap leading to atherothrombosis. Importantly, in all three of the hypotheses, TF expression is induced in atherosclerotic lesions with (1) the introduction of leukocytes in the subendothelial space [5, 21] and (2) modified LDL activation of receptor complexes on these leukocytes, VSMCs, and endothelial cells [22-28••].

High levels of TF are expressed in atherosclerotic plaques and is associated with both cellular (macrophages, VSMCs, and endothelial cells) and acellular (foam cell-derived debris within the necrotic core) regions [29-36]. Monocyte chemoattractant protein-1

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(MCP-1) is a potent chemokine involved in both the initiation and progression of atherosclerosis, and has been shown to induce TF expression in both monocyte/macrophages and VSMCs [37-38]. Aggregated LDL increases TF expression on human monocytes/macrophages resulting in the release of biologically active TF-positive MPs [22]. Further, oxLDL is a potent activator of TF in monocytes, VSMCs, and endothelial cells resulting in the release of TF-positive MPs, which are highly procoagulant [23-28••, 39]. Indeed, atherosclerotic plaques have 200-fold higher concentrations of leukocyte, VSMC, and endothelial cell-derived MPs compared with circulating blood [40]. Importantly, more than 50% of the MPs isolated from the plaques were TF-positive [40]. Finally, increased TF expression is correlated with the progression of human atherosclerotic lesions, more than likely due to an increase in macrophage apoptosis and necrosis as the lesion expands [36].

The TF:FVIIa complex not only triggers clotting but also activates the protease-activated receptor 2 (PAR-2), which results in proinflammatory signaling [41-42•]. TF induction of proinflammatory cytokines and chemokines can result in further leukocyte recruitment to the atherosclerotic lesion, thus enhancing the progression of atherosclerosis [6, 9, 13, 34]. VSMCs play a key role in atherosclerosis both in early and in late stages [43]. In early stages, VSMCs migrate from the media to the intima where they are trapped and proliferate to contribute to the development of fatty streaks. More advanced atherosclerotic lesions contain VSMCs that have a higher proliferative index and a greater synthetic capacity for extracellular matrix, particularly collagen, proteases and cytokines [44-46]. Similar to macrophages, late-stage VSMCs can express a variety of receptors for lipid uptake and can form foam-like cells, thereby participating in the accumulation of plaque lipid. Importantly, the presence of TF contributes to VSMC migration in vitro and in vivo [47], which appears to be due to the activation of the PAR-2 signaling pathway [48]. Further, TF:FVIIa activation of PAR-2 results in the secretion of the inflammatory cytokine IL-6 and chemokine IL-8, which further the atherogenic immune phenotype [49]. In addition, ligation of the CD40 receptor, implicated in the atherogenic immune process, on VSMCs and monocyte/macrophages can augment the expression of TF protein and activity in the atherosclerotic lesion [50-53]. These data suggest that TF may contribute to monocyte infiltration, macrophage foam cell formation, cyokine and chemokine production, and SMC migration to initiate and progress atherosclerosis.

Despite the plethora of in vitro studies supporting the idea that TF may contribute to the progression of atherosclerosis, it is important to note that the specific contribution of TF:FVIIa to atherosclerosis in mouse models remains uncertain. Our laboratory found that heterozygous TF mice ($TF^{+/-}$) expressing only 50% of the normal level of TF had similar amounts of atherosclerosis compared to $TF^{+/+}$ mice on an atherogenic apolipoprotein E ($Apoe^{-/-}$) background [54]. Similarly, a deficiency of TF in bone marrow cells did not affect atherosclerosis in a low density lipoprotein receptor deficient ($Ldlr^{-/-}$) mouse model [54]. It should be noted that the $Apoe^{-/-}$/low TF mice were not able to be studied due to premature death by 12 weeks of age and thus the contribution of non-hematopoietic TF could not be analyzed. Further, the $Apoe^{-/-}$ studies were conducted in 34 week old mice, which may have missed differences in the early stages of atherosclerosis. Additionally, $Apoe^{-/-}$ mice have defects in innate and adaptive immune response, independent of lipoproteins [55-56]. It is interesting that different results are observed with changes in levels of the natural inhibitor

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of TF called tissue factor pathway inhibitor (TFPI). For instance, a significant increase in atherosclerosis was observed in mice with a 50% reduction of TFPI ($Apoe^{-/-}/Tfpi^{+/-}$) compared to littermate controls [57]. Interestingly, a VSMC overexpressing TFPI mouse on an $Apoe^{-/-}$ background had less atherosclerosis [58••]. Finally, atherosclerotic studies utilizing PAR-2 deficient mice have not yet been conducted. Therefore, the role of TF:FVIIa and PAR-2 in atherogenesis needs further examination.

Role of TF in Plaque Rupture and Atherothrombosis

The most detrimental role of TF in atherosclerosis is the triggering of thrombosis after plaque rupture. Importantly, many studies have demonstrated TF in atherosclerotic plaques as the primary protein responsible for the thrombogenicity of the plaque and the primary cause of atherothrombosis [59-60]. While TF is associated with atherothrombosis, the extent of plaque thrombogenicity is dependent upon plaque composition. For example, TF present in plaques is associated with 60% of the cells in the atheroma, including: endothelial cells, VSMCs, and mostly monocyte/macrophages and foam cells [32-33, 36, 61-64]. Importantly, the level of TF in the plaque is strongly associated with plaque thrombogenicity [65]. In addition, Ardissino and colleagues demonstrated TF activity is higher in plaques from patients with unstable coronary syndromes and myocardial infarction versus patients with stable disease [66]. Further, the amount of TF protein in the plaque was correlated with TF activity [66]. However, some of the TF within the cellular milieu of the atheroma is associated with TFPI, and the presence of TFPI in human atherosclerotic plaques is associated with decreased TF activity [67-68, 69•, 70]. Importantly, a recent study demonstrated that lipoprotein (a) (Lp(a)), a complex of LDL and apolipoprotein a, can inactivate TFPI [71]. Lp(a) is a known risk factor for atherosclerosis, is upregulated in patients with unstable coronary syndromes, and accumulates in atherosclerotic plaques [72-73]. Therefore, the presence of Lp(a) may alter the TF/TFPI balance and increase the thrombogenicity of the plaque.

As mentioned previously, atherosclerotic plaques contain high levels of TF-positive MPs [40]. In addition, Mallat and colleagues demonstrated 97% of the total procoagulant activity extracted from atherosclerotic plaques was due to TF [74]. Subsequent proteomic analyses have demonstrated that over 90% of plaque-derived MPs are CD14 positive, suggesting monocyte/macrophage origin [75]. Bonderman and colleagues found increased TF activity associated with MPs taken from carotid atherosclerotic plaques [76]. Finally, Rautou and colleagues showed that plaque-derived MPs, but not circulating MPs, were able to activate endothelial cells resulting in leukocyte adhesion and transmigration [77••]. Together, these studies suggest that much of the TF that initiates atherothrombosis during plaque rupture is in the form of MPs.

It has been demonstrated that vessel wall TF is the primary cellular source that triggers thrombosis in animal models of arterial thrombosis [11, 78-79]. Importantly, carotid injury of atherosclerotic lesions in $Apoe^{-/-}/Tfpi^{+/-}$ mice demonstrated a decreased time to occlusion versus littermate controls and this was attributed to increased TF activity [57]. In addition, hyperlipidemia is associated with a shorter occlusion time in mouse carotid arterial thrombosis models [11, 28••, 80••-81]. The role of circulating TF-positive MPs in

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thrombosis can be evaluated using the laser-injury cremaster arteriole injury model. We recently, found that hematopoietic cell-derived, TF-positive MPs were increased during hyperlipidemic mice and enhanced thrombosis in this model [59]. Together, these studies indicate that TF and TF-positive MPs play a key role in thrombosis associated with atherosclerotic vessels.

TF-positive MPs as a Biomarker of Atherothrombotic Disease and Thrombotic Risk

MPs may serve as delivery vessels for certain proteins and nucleic acids (extensively reviewed in [82•]). However, many studies have demonstrated increases in certain MPs in a wide variety of disease states [83]. We believe that TF-positive MPs may serve as a potent biomarker of CVD and thrombotic risk.

Several studies have demonstrated an increase in expression of monocyte TF, monocyte-derived TF-positive MPs, and MP TF activity in the plasma of patients with hypercholesterolemia [28••, 80••, 84-86]. In addition, TF antigen, circulating procoagulant MPs, and TF-positive MPs are increased in patients with unstable angina, myocardial infarction, and patients undergoing angioplasty or coronary stenting [87-90]. Importantly, MP TF activity is increased in patients with acute myocardial infarction and atherosclerotic plaques [89, 91-92]. The role of TF-positive MPs in CVD and atherothrombosis has been extensively reviewed [80••, 93••]. Together, these studies suggest that levels of TF-positive MPs, likely derived from activated monocytes, are increased in patients with CVD. However, unlike our recent finding that prospective analysis of MP TF activity can be predictive of venous thromboembolism (VTE) in patients with pancreatic cancer [94], further studies are needed to demonstrate the predictive value of MP TF activity in patients with CVD.

To address this question in an experimental model, we recently demonstrated that prolonged hypercholesterolemia, a known risk factor for atherosclerosis, results in a step-wise increase in the activation of coagulation, as measured by thrombin-antithrombin (TAT) and D-dimer, in both mice and monkeys [28••]. Moreover, we demonstrated that MP TF activity was also increased in a step-wise manner and was correlated with TAT, increased levels of oxLDL, and the inflammatory cytokine IL-6 [28••]. Importantly, levels of peripheral blood mononuclear cell (PBMC) TF were also increased with prolonged hypercholesterolemia. We further demonstrated that TF inhibition with an anti-TF antibody ablated the activation of coagulation and MP TF activity. Finally, we used bone marrow transplantation to demonstrate that TF-positive MPs were derived from hematopoietic cells. Together, we suggest that monocyte-derived TF is responsible for the systemic activation of coagulation and that MP TF activity serves as a potent biomarker of this response. While we did not examine atherosclerotic burden at each of the time-points, several studies have demonstrated progression of atherosclerosis in the $Ldlr^{-/-}$ model during the time-course utilized in our study [95-96]. This would suggest that circulating MP TF activity is likely to correlate with the level of atherosclerosis.

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Potential Therapeutic Inhibition of TF and TF-induction of Thrombin and Fibrin in Atherothrombosis

First line therapy for patients with advanced atherosclerosis and patients discharged post myocardial infarction usually includes administration of: (1) statins to lower LDL cholesterol and niacin or fibrate to raise HDL [97-98], (2) antiplatelet therapy consisting of aspirin or clopidogrel, (3) blockade of the renin angiotensin system via an angiotensin converting enzyme (ACE) inhibitor with or without an angiotensin II receptor blocker (ARB), and (4) administration of beta blockers [99]. However, statins also exhibit several pleiotrophic properties, such as anti-inflammatory responses and inhibition of prenylation of intracellular signaling proteins [100-101]. Importantly, statins have also been demonstrated to reduce TF expression and activity, both in vitro and in vivo, in several animal models of atherosclerosis and hypercholesterolemia as well as in humans [24, 26, 28••, 85-86, 100, 102-105] .

We recently demonstrated that oxLDL induction of TF in human monocytes is inhibited by pretreatment with simvastatin [28••]. In addition, simvastatin administration attenuated hypercholesterolemic increases in oxLDL, PBMC or white blood cell TF, MP TF activity, circulating MPs, and thrombin-antithrombin (independent of changes in LDL) in both mice and monkey study models [28••]. Similar LDL-independent effects of simvastatin and pravastatin resulted in reduced inflammation and thrombogenicity in hypercholesterolemic pigs and monkeys [106-107]. Regarding atherosclerosis, simvastatin and rosuvastatin administration reduced both aortic and atherosclerotic lesion TF in hypercholesterolemic mice without affecting LDL [100, 102]. Importantly, monocyte and macrophage expression of TF is inhibited by statins [24, 26, 85-86, 103-105]. This statin-induced reduction of TF is also demonstrated in vivo in type II familial hypercholesterolemic patients along with concomitant reductions in prothrombin fragmant F1 + 2 [85-86]. These data suggest that simvastatin can decrease TF expression and activity, primarily in monocytic cells, and that this may be an alternative therapy for TF inhibition in atherosclerotic and atherothrombotic conditions.

It is interesting to note that almost 50% of patients who develop atherosclerosis and eventual atherothrombosis have levels of LDL cholesterol which are considered at or below the average range of an otherwise ‘healthy’ population [17, 108]. Therefore, these patients could also benefit from the pleotrophic effects of statin therapy [100-101]. The key is to identify these ‘normal’ patients with advanced atherosclerotic disease using various other biomarkers, e.g. TF-positive MPs (as discussed in the previous section), and with screening of inflammatory markers. In a hallmark study, the justification for the use of statins in primary prevention (JUPITER) trial demonstrated preemptive administration of rosuvastatin to individuals with normal levels of LDL, but elevated levels of inflammation, could significantly reduce the incidence of major cardiovascular events [109]. Again, this demonstrates that inflammation may serve as a potent biomarker in patients with ‘silent’ atherosclerotic disease having normal lipid levels. In addition, a retrospective analysis of JUPITER found that VTE was also significantly reduced in this patient population [110••]. It

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was speculated that this reduction in events was due to statin-induced inhibition of TF expression [110••].

In addition to statins, another commonly used therapeutic also reduces both direct TF expression and activity in vitro and in vivo. Application of ACE inhibitors captopril, idrapril, and fosinopril, as well as the ARB losartan, dose-dependently decreased TF expression and activity in endotoxin-stimulated PBMCs [111]. Interestingly, ACE inhibition with enalapril also decreased levels of plasma TF antigen in patients with acute myocardial infarction [112]. Moreover, ACE inhibitors have been demonstrated to reduce the incidence of myocardial infarction, suggesting potential antithrombotic effects of this drug class [113-116]. This may occur, in part, independently of blood pressure inhibition by decreasing synthesis of IL-1β and TNF-α recruitment of monocytes to atherosclerotic plaques [111, 117-118]. Together, this data suggests ACE inhibitors and ARBs may have similar pleiotrophic effects to statins and that their antithrombotic outcomes may be, in part, due to reduced TF expression in monocytes.

Conclusion

In summary, high levels of TF are present in atherosclerotic plaques. Importantly, plaque-derived TF is likely to be a major trigger of atherothrombosis and is the major determinant of the thrombogenicity of the atheroma. TF-positive MPs are generated in advanced atherosclerosis and may be a useful biomarker for monitoring atherosclerosis and thrombotic risk. Finally, there are several clinically used drugs that inhibit TF expression and this may add to the beneficial effects of these drugs.

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